

FORM PTO-1390  
(REV. 1-98)

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER

20066-10

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

PRIORITY DATE CLAIMED

September 16, 1996

INTERNATIONAL APPLICATION NO.

PCT/IL97/00232

INTERNATIONAL FILING DATE

July 9, 1997

TITLE OF INVENTION

DRUG-DEVICE COMBINATION FOR CONTROLLING THE CONTRACTILITY OF MUSCLES

APPLICANT(S) FOR DO/EO/US

Shlomo BEN-HAIM, Nissim DARVISH, Yuval MIKA, Maier FENSTER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expire
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes of the International Preliminary Examination Report under PCT Article (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.  
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

International Search Report

EXPRESS MAIL No. EI007668465US - March 12, 1999

17. <input type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1070.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$930.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$790.00  International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$720.00  International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$98.00  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>CALCULATIONS PTO USE ONLY</b>	
				\$	670.00
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	69 - 20 =	49	x <del>\$22.00</del> 18.	\$	882.00
Independent claims	6 - 3 =	3	x <del>\$62.00</del> 78.	\$	234.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ <del>\$70.00</del> 260.	\$	260.00
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$	2046.00
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				\$	
<b>SUBTOTAL =</b>				\$	2046.00
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
<b>TOTAL NATIONAL FEE =</b>				\$	2046.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$	
<b>TOTAL FEES ENCLOSED =</b>				\$	2046.00
				Amount to be refunded:	\$
				charged:	\$

a. ☒ A check in the amount of \$ 2046.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees.  
A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any  
overpayment to Deposit Account No. 03-3415 . A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR  
1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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1133 Avenue of the Americas  
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09/254993

610 Rec'd PCT/PTO

12 MAR 1999  
20066-10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

SHLOMO BEN-HAIM et al.

Serial No.: to be assigned

Filed: to be assigned

For: DRUG DEVICE COMBINATION FOR CONTROLLING  
THE CONTRACTILITY OF MUSCLES

March 12, 1999

Box DO/EO/US  
U.S. Patent and Trademark Office  
Washington, D.C. 20231

PRELIMINARY AMENDMENT

S I R :

Prior to calculation of the filing fee and examination,  
please amend the above-referenced application as follows:

IN THE CLAIMS:

Claim 25, line 1, change "any one of claims" to -- claim --,  
and change "to 24" to -- or 13 --.

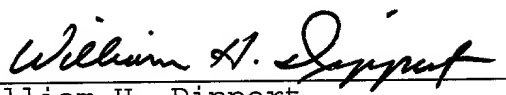
At line 1 of each of Claims 37 to 41, change "29 to 36" to  
-- 29, 30, and 36 --.

Claim 46, line 3, change "1 to 29" to -- 1, 13, and 26 --.

At line 1 of each of Claims 47 to 50, change "1 to 26" to  
-- 1, 13, and 26 --.

Cancel Claim 51 without prejudice.

Respectfully submitted,

  
William H. Dippert  
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09/254993

DRUG-DEVICE COMBINATION FOR CONTROLLING THECONTRACTILITY OF MUSCLES

510 Rec'd PCT/PTO 12 MAR 1999

Field of the Invention

The present invention relates to the field of medicine. More particularly, the invention relates to means for controlling the contractility of muscles in patients treated with drugs which influence the cardiovascular system.

Background of the Invention

Many activities of the human body involve the contraction of muscles. For instance, movement of the limbs, breathing activity, etc. The most complex and vital muscular activity of the human body is that of the heart, which functions as a pump and which, by contracting at the required times and in the required manner, controls the flow of blood throughout the body.

The heart is composed of different parts, which contract differently and with different timing, in order to permit the aforementioned pumping activity. The contraction of the heart is controlled by electric stimuli, which are generated at the cellular level by chemical reaction. However, it is well known in the art to control the timing of the contraction of the cardiac muscle, by the action of externally applied electric stimuli, through the so-called "pace maker".

In a copending PCT patent application No. PCT/IL97/00012, filed January 8, 1997 by the same applicants herein, the specification of which is incorporated herein by reference, there is described a method and apparatus for modifying the force contraction of at least a portion of a heart chamber, which comprises applying a non-excitatory electric field, for a predetermined period of time, at a delay after activation, which causes the force of contraction to be increased. Substantial increases in the force of contraction are obtained, typically - but non-limitatively - in the order of 5% - 50%. This increase in cardiac output is useful in order to obviate cardiac insufficiency due to a variety of pathological situations, e.g., the reduction of cardiac output due to the implantation of a pace maker, the insufficiency due to the results of the malfunctioning of a portion of the cardiac muscle, etc.

In another copending PCT/IL patent application, entitled "Apparatus and Method for Controlling the Contractility of Muscles", filed by the same applicants herein on the same day as the present application and identified as Attorney's Docket 4224/WO/97, the specification of which is incorporated herein by reference, there is described a method and apparatus for decreasing the force contraction of at least a portion of a heart chamber, which comprises applying a non-excitatory electric field of a polarity inverse of that required for obtaining an increase of muscle contractility, for a predetermined period of time, at a delay after

activation, which causes the force of contraction to be decreased. The ability of reducing the contractility is of importance in a variety of situations, e.g., during surgery or as an aid in healing of hibernated areas of a heart after myocardial infarct.

Several severe diseases of the cardiac muscle cannot be treated effectively without the aid of drugs. However, many drugs used in therapy have a deleterious side-effect in that they reduce the contractility and cardiac output of the heart and may cause life threatening arrhythmias. Some illustrative examples of drugs used in the treatment of congestive heart failure (CHF) are given below.

Congestive heart failure (CHF) is a complex clinical syndrome characterized by impaired ventricular performance, exercise intolerance, a high incidence of ventricular arrhythmias, and shortened life expectancy. Virtually all forms of heart disease can lead to heart failure, with coronary artery disease, hypertension, and diabetes mellitus being the most common in the U.S.

CHF can be broadly subdivided into two distinct forms (although several other classification schemes have been used). Distinguishing between the two forms is often difficult: 1. Diastolic dysfunction or diastolic heart failure; and 2. Systolic dysfunction or systolic CHF.

Changes in the structure and biochemical properties of the myocardium and peripheral vasculature occur during the development of CHF and these changes can contribute to further impairment of cardiovascular function. Many different drugs are used in the therapy of CHF, which affect the cardiac muscle, whether directly or indirectly, by causing changes in the cardiovascular system.

Recent studies indicate that metoprolol, a commonly used beta-blocker which can cause up-regulation of beta-1 receptors, can restore catecholamine responsiveness to patients with dilated cardiomyopathy.

Captopril, an ACE inhibitor that is commonly used to treat heart failure, has been shown to increase lymphocyte Gs and increase myocardial beta-1 receptor density.

Digitalis (cardiac glycosides): has been used clinically for over 200 years to treat heart failure and edema (dropsy), but its present use in treating CHF is controversial. Digoxin is the most widely used preparation of digitalis (half-life = 1-2 days), although digitoxin (half-life = 7 days) is also used in situations where long half-life may be an advantage.

However, Digoxin may be toxic at relatively low dosages, since it may cause arrhythmia and conduction problems, but the art has so far failed to



provide means by which the desirable therapeutic effect of Digoxin or similar drugs may be maintained at low dosages, so as to avoid toxicity problems.

Beta-Adrenergic agonists: beta1-adrenergic agonists (dopamine, dobutamine, prenalterol, xamoterol) have been used to treat acute and chronic heart failure, but have limited usefulness in chronic CHF because of their arrhythmogenic effects, short duration of action, the development of tolerance, and necessity of parenteral administration.

Dobutamine is a moderately selective beta1-adrenergic agonist that lacks vasoconstrictor activity and causes minimal changes in heart rate. It is frequently added to nitroprusside when blood pressure is adequate to increase cardiac output.

Prenalterol and xamoterol are partial beta1-adrenergic agonists that may simultaneously stimulate beta1-receptors and block the receptors from stimulation by endogenous catecholamines, thereby protecting against beta1-receptor down-regulation.

Cyclic nucleotide phosphodiesterase (PDE-III, cGMP-inhibitable PDE)

inhibitors: There are several agents that increase myocardial and vascular smooth muscle cAMP through inhibition of cyclic nucleotide

phosphodiesterase PDE-III, cGI PDE) activity. These agents should therefore simultaneously increase cardiac output and reduce afterload.

The bipyridines, amrinone and milrinone, are potent PDE-III inhibitors that can be given orally or parenterally. They can be given orally, are generally well-tolerated, but can have significant non-cardiac side-effects (nausea, vomiting, thrombocytopenia).

Ca<sup>+</sup> Channel Blockers: Ca<sup>+</sup> channel antagonists are widely used in many types of heart diseases, including cardiac insufficiency, and cause direct arterial vasodilatation by the inhibition of Ca<sup>+</sup> current. Diltiazem and Verapamil exhibit negative inotropic, chronotropic and dromotropic effect on cardiac function. Some of these drugs, such as Verapamin, have life threatening side effects, such as altering the A-V node conduction.

Anti-Arrhythmic Drugs: In cardiac insufficiency, and in other ischemic diseases, many patients suffer from arrhythmia. Drugs acting on the chronicity are known to cause many side effects.

It is therefore clear that it is highly desirable to be able to reduce the dosage of such drugs, whenever possible, or to obviate side effects and problems which they may cause.

It has now been surprisingly found, and this is an object of the present invention, that it is possible to obviate the aforementioned drawbacks of drugs used in the therapy of heart diseases, by applying a non-excitatory signal of the type described above, which increases the contractility of the cardiac muscle and its output. It has further been found that this can be achieved without generating adverse effects and/or without adversely affecting the activity of the drug which is administered to the patient.

It is an object of the invention to provide apparatus for the combined drug/electric-stimulation treatment, which can be used as a treatment aid for a patient in need of a medicine which impairs heart muscle contractility.

It is another object of the invention to provide a method for treating a patient in need of a drug which may impair the contractility of the heart muscle.

It is yet another object of the invention to provide apparatus useful in therapy, by means of which the dosage of drugs having potentially harmful side effects can be reduced or, alternatively, by means of which the dosage can be increased while keeping side effects within an acceptable range.

It is still another object of the invention to provide apparatus which cooperates with such drugs, its activity being related to the amount of the drug present at a given time in the patient's blood.

Other objects and advantages of the invention will become apparent as the description proceeds.

### SUMMARY OF THE INVENTION

In one aspect, the invention relates to an apparatus for the combined drug/electric-stimulation treatment of a cardiac muscle, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of a muscle.

According to a preferred embodiment of the invention, the apparatus comprises circuitry for controlling the start time of the electric potential generated between said at least two points. According to another preferred embodiment of the invention the apparatus comprises circuitry for controlling the duration of the electric potential generated between said at least two points. According to still another preferred embodiment of the invention the apparatus comprises circuitry for controlling the magnitude of the electric potential generated between said at least two points.

In a preferred embodiment of the invention the circuitry for creating a non-excitatory electric potential between said at least two points comprises one or more electrode. A variety of different electrodes can be used, which will be easily recognized by the skilled person. An illustrative example of suitable electrodes are carbon electrodes.

In another aspect, the invention is directed to apparatus for the combined drug/electric stimulation treatment, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of a muscle.

According to a preferred embodiment of the invention, the apparatus comprises circuitry for controlling the start time of the electric current flowing between said at least two points.

According to another preferred embodiment of the invention, the apparatus comprises circuitry for controlling the duration of the electric current flowing between said at least two points.

According to still another preferred embodiment of the invention, the apparatus comprises circuitry for controlling the magnitude of the electric current flowing between said at least two points.

In a preferred embodiment of the invention the circuitry for causing a non-excitatory electric current to flow between said at least two points comprises one or more electrode, e.g., carbon electrodes.

In another aspect the invention is directed to means and methods for counteracting proarrhythmic effects of drugs.

In the context of the present invention, by "non-excitatory current", or "non-excitatory potential", or "non-excitatory signal", it is meant to indicate a signal which does not cause a propagating action potential in the muscle cells (which may start a new pacing or contraction of the muscle). In other words, the non-excitatory electric stimulation effected by a non-excitatory electric pulse is such that it does not induce propagating activation potentials in the cardiac muscle cells. Rather, such pulses affect the response of the heart muscle to the action potentials, by modulating cell contractility within selected segments of the cardiac muscle. As described in the abovementioned PCT patent application PCT/IL97/00012, the inventors have found that by applying non-excitatory electrical stimulation pulses of suitable strength, appropriately timed with respect to the heart's electrical activation, the contraction of the selected segments can be increased or decreased, thus increasing or decreasing the stroke volume of the heart.

There may be various reasons for a signal to be non-excitatory. Two main types of non-excitatory signals to be used in conjunction with the invention are: 1) A signal which, independently of its magnitude, is applied during the refractory period, and therefore does not cause a new contraction, even though its magnitude may be above threshold values for pacing; 2) A signal which is sub-threshold for pacing and, therefore, no matter when given, does not cause a new contraction to take place.

While a DC current is typically used as the base line for the non-excitatory signal, it is possible to supply a signal which is a complex signal, for instance, a signal generated by superimposing an AC current on the DC base signal, so as to generate a waveform of varying envelope. Any suitable signal can be superimposed, having any shape, e.g., square wave or sinusoidal wave, as will be apparent to the skilled person. Thus, according to one preferred embodiment of the invention the apparatus further comprises means for superimposing on a DC signal one or more waveforms of given frequency and amplitude, thereby to generate a complex signal.

The apparatus of the invention can be provided in different forms, e.g., as an insertable device or an extra corporal device or an implantable device.

According to a preferred embodiment of the invention, the circuitry for controlling the start time and/or duration of the electric potential is

synchronized to heart activity, for instance, it can operate not at every beat of the heart, e.g., every 1, 2 or 3 beats of the heart.

According to a preferred embodiment of the invention the non-excitatory electric current is a DC electric current, and the apparatus may further comprise circuitry for superimposing on the DC signal one or more waveforms of given frequency and amplitude, thereby to generate a complex signal.

The apparatus employed to carry out the method of the invention can be of different construction, as will be apparent to the skilled person. One example of apparatus suitable for carrying out the invention is described in detail and claimed in a copending PCT patent application of the same applicants herein, entitled "Cardiac Output Controller", filed on the same day as the present application and identified as Attorney's Docket 27068, the description of which is incorporated herein by reference. Another example of suitable apparatus, coupled to a pacemaker device, is the subject of another copending PCT patent application of the same applicants herein, entitled "Cardiac Output Enhanced Pacemaker", filed on the same day as the present application and identified as Attorney's Docket 27181, the specification of which is also incorporated herein by reference. However, as said, the invention is not intended to be limited to any particular construction of device used to carry it out.



In another aspect, the invention is directed to apparatus for the combined drug/electric-stimulation treatment of a cardiac muscle, comprising:

- means for creating an electric potential between at least two points located in the vicinity of the cardiac muscle;
- means for causing a non-excitatory electric current to flow between said at least two point; and
- means for controlling the start time, duration and magnitude of the electric current flowing between said at least two points.

According to a preferred embodiment of the invention the apparatus comprises:

- means for creating an electric potential between at least a pair of electrodes in the vicinity of the cardiac muscle at at least two root locations;
- means for causing a non-excitatory electric current to flow between said at least two root locations; and
- means for controlling the start time, duration and magnitude of the electric current flowing between said at least two root locations.

By "root location" it is meant to indicate the vicinity of the muscle where the electrodes are located, which may be distinct from the area which is affected by the current flowing between them. As will be appreciated by the skilled person, due to the very complex nature of the electric behavior

of the cardiac muscle, it is possible that positioning an electrode at a given location will affect another, more remote portion of the muscle. Therefore, the root location is not necessarily the center or any other portion of the treated area, but it is only a location, near the muscle, where an electrode will be positioned.

The invention is further directed to a method for the combined drug/electric stimulation treatment of a cardiac muscle, comprising a) administering to a patient in need thereof a drug which affects the cardiovascular system and which affects the cardiac muscle, or a mixture of two or more such drugs, b) creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and c) controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points.

In another aspect the invention is directed to a method for the combined drug/electric stimulation treatment of a cardiac muscle, comprising a) administering to a patient in need thereof a drug which affects the cardiovascular system and which affects the cardiac muscle, or a mixture of two or more such drugs, b) causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and c) controlling one or more of the parameters consisting of start time,

duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points.

The signal supplied to the patient according to the method of the invention is of the same type as described above with reference to the apparatus.

The change in cardiac muscle contractility and of electrophysiological characteristics of the cardiac muscle obtained by the method of the invention can be exploited for a variety of therapeutic purposes. According to one preferred embodiment of the invention, it is designed at least partially to compensate for cardiac muscle contractility decrease induced by said drug or mixture of drugs. According to another preferred embodiment of the invention it is designed at least partially to compensate for cardiac muscle contractility increase induced by said drug or mixture of drugs. According to still another preferred embodiment of the invention the change in cardiac muscle contractility is designed to add to and/or amplify the cardiac muscle contractility increase or decrease induced by said drug or mixture of drugs.

In another aspect the invention is directed to a method for reducing the dosage of a cardiovascular drug which affects cardiac muscle contractility. Thus, drugs such as Digoxin, and other proarrhythmic drugs, which as explained above have serious side effects, can be administered in

substantially lower dosages, while at the same time achieving the same or even an improved effect on cardiac muscle contractility.

Thus, according to a preferred embodiment of the invention there is provided a method for the combined drug/electric-stimulation treatment of a cardiac muscle, comprising:

- administering to a patient in need thereof a drug which affects the cardiovascular system and which affects the cardiac muscle, or a mixture of two or more such drugs;
- providing an electric potential between at least a pair of electrodes in the vicinity of the cardiac muscle at at least two root locations;
- causing a non-excitatory electric current to flow between said at least two contacting locations; and
- controlling the start time, duration and magnitude of the electric current flowing between said at least two root locations, so as to impart the desired change in cardiac muscle contractility.

The invention further encompasses a kit for the treatment of cardiovascular diseases, comprising a drug or a combination of two or more drugs, and an apparatus according to the invention, as herein described.

Additional apparatus according to the invention comprises circuitry for controlling its activity as a function of calculated and/or actual level of a given drug or combination of drugs in the patient's blood.

The apparatus of the invention is further useful for reducing the dosage of pro-arrhythmic drugs, and, for counteracting side-effects of pro-arrhythmic drugs.

Further therepeutic flexibility can be provided by another preferred embodiment of the invention, in which the apparatus comprises timing circuitry for activating it at predetermined times during the day.

As will be appreciated by the skilled person, the actual set of operating parameters used (current, length of pulse, number of electrodes, lag after pacing signal, etc.), will be dependent on the specific use made of the invention, and the skilled person will be able to devise the optimal set of parameters for a given application. Some non-limitative operating ranges in which cardiac muscle reacts according to the invention are given here for the sake of illustration only, it being understood that operation outside such ranges is of course possible under various conditions: Current: 0.01 - 10 mA; Length of Pulse: 1-998 milliseconds with a pacing of 1 Hz, and 1-498 milliseconds with a pacing of 2 Hz; Delay after Pacing Signal: 1 milliseconds and above. Where no pace maker is used, the delay is

preferably calculated from the natural pacing of the patient's heart, or from the local activation time.

While a variety of electrodes can be used, and the invention is in no way limited to any particular type of electrode, particularly preferred suitable electrodes for this purpose are, e.g., carbon electrodes.

### Brief Description of the Drawings

The above and other characteristics and advantages of the invention will be more readily apparent through the following detailed description of preferred embodiments thereof, with reference to the appended drawings, wherein:

Fig. 1 shows the effect of the application of an NT-signal to a rabbit papillary muscle in the presence of Caffeine;

Fig. 2 shows the effect of the application of an NT-signal to a rabbit papillary muscle in the presence of Ryanodine;

Fig. 3 shows the effect of the application of an NT-signal to a rabbit papillary muscle in the presence of Nifedipine;

Fig. 4 shows the effect of the application of an NT-signal to a rabbit papillary muscle in the presence of both propranolol and adrenaline;

Fig. 5 shows the effect of the application of an NT-signal to a rabbit papillary muscle in the presence of adrenaline;

Fig. 6 shows the effect of the application of an NT-signal to a rabbit papillary muscle in the presence of Diltiazem;

Fig. 7 shows the effect of the application of an NT-signal to a rabbit papillary muscle in the presence of Digoxin; and

Fig. 8 is a schematic representation of an apparatus according to one embodiment of the invention.

### Definitions

The following terms and abbreviations, used throughout this specification, are defined below, for the sake of clarity:

b.p.m. = Beats per minute

HMC = Hypertrophic Cardiomyopathy

I.M. = Intramuscular

IV = Intra Venous

LV = Left Ventricle

LVP = left ventricular pressure

NT Signal= Non-Excitatory Signal

RV = Right Ventricle

VF = Ventricular Fibrillation

### Detailed Description of Preferred Embodiments

The invention will now be illustrated through detailed experiments. Experiments *in vitro* were carried out using isolated rabbit papillary muscle, and the protocol for its isolation is detailed below.

### Equipment

The following equipment which will be referred to hereinafter, is now briefly described for the sake of clarity:

Plugsys system: The plugsys system is an incorporating plug in modules for measuring, controlling and data processing in connection with recorders and computers. In general, it functions as an amplifier which increases the sensitivity of the measuring of biological signals. One such device, used in the experiments described herein, is manufactured by HSE, Germany.

Millar: This device (manufactured by Millar Instruments, USA), is a micro manometers transducer that can be connected to a battery operated bridge (which is the interface box) and the output can be digitized using an A/D converter. In another mode of operation the transducer is connected through a DBA (plugsys DC Bridge Amplifier), which is an amplifier connected to transducers to measure pressure force (manufactured by



HSE, Germany).

### Isolated Papillary Muscle Protocol

**Animals:** New Zealand white rabbits (males) from Israel (Yokneam) or an hybrid of New Zealand White and local albino rabbits (males, AniLab, Rehovot) are kept in room temperature, 2-3 per cage (35x55x65 cm), under natural light conditions. Daily feeding of dry food (Rabbit Mix- Code 590), and unlimited water supply. The cages and the room are cleaned daily,

### Instruments:

**A. for solution making:** Scales (by Mettler toledo, model P8303, Max 310gram, d=1mGram) magnetic stirrer. by Freed electric. Weights 10Kg (d=50gram) by Moznei Shekel, Gas tanks with mixed 95% O<sub>2</sub> +5% CO<sub>2</sub>" pressure regulators, pH meter by Mettler toledo, model 320 PH, ice machine 45 Labotal.

### **B. for the in-vitro papillary muscle preparation**

Dissection chamber (HSH, Hugo Sachs Elektronik, Germany), Steered organ bath type 813 (I-18E) including temperature controller type 319, Force Transducer type F30 with amplifier type 660 and calibration unit (HSE), Stereoscope (Olympus), Digital micro manipulator (HSB), Manipulator, Anti- vibration table (TMC, USA), Faraday cage, Fiber optic illuminator (HSE), Current and Voltage clamp amplifier (axon

Instruments, USA), stimulators (Grass instruments, USA), Micro- pipette puller by Narishige (model pp-83, Japan) Current source ISO 10 and ISO - 50 (home made) supplying 10 and 50mA correspondingly and Oscilloscope, 20MHz (Gould, England), Computers: PowerPC 9500/I50, (Apple, USA), or Pentium, 160MHz, Data Acquisition Boards: PC-AO- 2DC, 16 bite, or the PCI-M10 8, 12 bite board by National Instrument, software: LabView for windows, by National Instrument (USA). Data acquisition and analysis program are home made, The program includes data acquisition and on-line analysis, programmable experiment execution, programmable signal output. The off-line analysis program analyze different parameters of muscle twitch and action potentials.

### Solution:

The Krebs-Heseleit Solution (KHS) was prepared using materials from Sigma (Israel): 0.32 g/lit KCl (4.5 mM), 6.99 g/lit NaCl (118.0 mM), 2.01 g/lit NaHCO<sub>3</sub> (24.0 mM), 0.285 g/lit MgSO<sub>4</sub>•7H<sub>2</sub>O (1.19 mM), 0.16 g/lit KH<sub>2</sub>PO<sub>4</sub> (1.18 mM), 2.0 g/lit Glucose (11.0 mM), and 0.37 g/lit CaCl<sub>2</sub>•2H<sub>2</sub>O (2.52 mM), added after bubbling with a 95% O<sub>2</sub> + 5% CO<sub>2</sub> gas mixture for 20 minutes.

Solution preparation: Distilled water (ion exchange column Zilion, Israel and ultra filtration by EasypurLF, Israel) are used to prepare the KHS stock solution (X 20, 5L). The chemicals listed above except CaCl<sub>2</sub> are

used. The stock solution expires after 1 week of refrigeration. For each day of experiment fresh solution is prepared (5L) out of the stock solution,  $\text{CaCl}_2$  is added, and the solution is bubbled (95%  $\text{O}_2$ /5%  $\text{CO}_2$ ) for 20 min. and titrated to a pH of 7.4. Bubbled KHS at room temperature is used for perfusion of the papillary muscle kept in the Steiert organ chamber. Ice cold (4 C), bubbled KHS is used for the dissection of the papillary muscles.

**Anesthesia and heart dissection:** animal is brought from the cage to a scale for measuring body weight. The animal is anesthetized by 1Vembutal 1-1.2 mg /Kg body weight I.P, using -5cc syringe and 23 Gage needle. The level of anesthesia is checked by the animal reflex to a pinch. When the animal is deeply anesthetized, the skin over the chest is cut off and the chest wall is cut exposing the heart. Using seizures and a forceps the pericardium is cut and the heart is dissected out by cutting all the blood vessels. Immediately after cutting, the heart is placed in an ice cold and oxygenated KHS.

**Papillary muscle dissection:** The heart is transferred to a fresh ice-cold KHS and then to the dissection chamber, containing ice-cold continuously oxygenated KHS. The heart is fixed to a rubber pad with insect pins and then the left ventricle is opened exposing the papillary muscles. A silk (6 0) thread is tight around the tendon of the papillary muscle and the muscle is dissected out using fine twizers. The dissected muscle (length of 2-3mm) is transferred to the organ bath and the heart is kept in the

dissection chamber at 4°C for further dissections of the other papillary muscles. The dissection of the papillary muscle last for 3-5 min.

**The Steiert Organ Bath:** The muscle is placed in an organ bath, and than fixed to the chamber by a plastic holder. The silk thread tight to the tendon is hooked to a rigid hook on the force transducer (on the opposite side) to give an isometric conditions. The papillary muscle is continuously perfused (7- 12ml/min,) with oxygenated KHS kept at a regulated temperature of 37°C.

#### Pacing and Stimulation:

Pacing stimuli (typically 1Hz, 2ms duration, and amplitude of 2mA) are given by two Ag-AgCl electrodes which are part of the organ bath and are placed under the muscle. The electrodes are covered with AgCl layer, chlorodizing by 5mA, 5ms pulses during perfusion. Constant current stimuli (CCU) are given to the upper part of the muscle using graphite electrodes (diameter of 0.5mm fitted to a glass pipette) placed 2-3mm apart along the fibers' line(contraction axis). The muscle length is adjusted to maximal isometric force and left for equilibration period of 30 min.

#### Drug administration:

We use the perfusion system for drug application by switching the feeding krebs solution bottle to the drug containing bottle. The drug is

administered for a period of 30-80 minutes while monitoring the mechanical and electrophysiological response of the muscle every 10 minutes.

### Example 1

#### Stimulation in the presence of Caffeine

A rabbit papillary muscle was stimulated by an NT-signal in the presence of Caffeine 10mM( Phosfodiesterase Inhibitor ).

A rabbit papillary muscle was stimulated in Organ-Bath perfused by KHS (normal experimental medium) together with Caffeine 10mM (which is a PDE inhibitor and also causes depletion of the internal cardiac  $\text{Ca}^+$  stores - Sigma, Mo, catalog No. C-8960) for 60 min before applying the NT signal.

The NT-signal applied to the electrodes<sup>4</sup> produced an average increase in peak force of the control. Caffeine 10mM when applied cause a significant reduction in the basal contraction force (33 % decrease). It also reduced the increase in peak force in response to NT stimulation applied to the same preparat in the presence of Caffeine to an average increase of 15 % in the muscle force, vs 60% increase in the control level.

#### Parameters:

Pacing: 1 Hz, 2mS Duration, 1mA current.

NT signal: 30mS Delay, 60mS Duration, 6mA, with the polarity increasing muscle contractility.

Temp. 36.2°C

The results are shown in Fig. 1.

### Example 2

#### Stimulation in the presence of Ryanodine

A rabbit papillary muscle was stimulated in Organ-Bath perfused by KHS together with Ryanodine (a Ca-release suppresser from the Sarcoplasmic Reticulume). 100nM (Sigma, Mo, catalog No. R-6017) for 60 min before applying the NT signal.

The NT-signal applied to this preparat produced an average increase in peak force of 60% in the control. Ryanodine 100nM when applied cause a significant reduction in the basal contraction force (55% decrease). However when NT stimulation was applied to the same preparat in the presence of Ryanodine, it produced an average increase of 70% in the muscle force, compared to the new basal force.

#### Parameters:

Pacing: 1 Hz, 2mS Duration, 1mA current.

NT Signal: 30mS Delay, 60mS Duration, 6mA.

Temp. 36.2°C

The results are shown in Fig. 2.

### Example 3

#### Stimulation in the presence of Nifedipine

A rabbit papillary muscle was stimulated in Organ-Bath perfused by KHS together with Nifedipine (Ca-channel blocker commonly used in clinical treatment in ischemic heart disease mainly affecting the smooth muscle cells in vascular vessels). 1 $\mu$ M (Sigma. Mo, catalog No. n-7634) for 10 minutes before applying the NT Signal.

The NT signal applied to this preparat produced an average increase in peak force of 30% in the control. Nifedipine 1 $\mu$ M when applied cause a significant reduction in the basal contraction force (70% decrease). However when NT stimulation was applied to the same preparat in the presence of Nifedipine an average of 35% increase in the muscle force was observed.

#### Parameters:

Pacing: 1 Hz, 2mS Duration, 1mA current.

NT Signal: 30 mS Delay, 60 mS Duration, 6mA.

Temp. 36.2°C

The results are shown in Fig. 3.

#### Example 4

##### Stimulation in the presence of Propranolol and Adrenaline

An experiment combining two drugs was carried out, the results of which are shown in Fig. 4. A rabbit papillary muscle was exposed for 5 minutes to propranolol (0.5  $\mu$ M) and adrenaline (0.25  $\mu$ M) in control (low amplitude trace) and activated by the NT signal (high amplitude trace).

The graph depicts twitches of papillary muscle after 5 min exposure to the above. The concomitant presence of the drugs decreased the overall muscle force. When the NT signal was applied, the contractile force increased by about 200%. The control trace reflects the clinical state of heart failure, with reduced contractility, high plasma catecholamine concentration, while there is down regulation of the Beta receptors.

##### Parameters:

pacing: 1Hz, 2 mS duration, 3 mA.

NT Signal: 30 mS delay, 60 mS duration, 6 mA.



Example 5Stimulation in the presence of Adrenaline

An experiment was carried out on a rabbit papillary muscle, in the presence of adrenaline, and the results are shown in Fig. 5. This graph is composed from two different triles on the same papillary muscle (left, rabbit). In the control turning on the NT signal caused an increase of about 110%, then adrenaline, 0.5 $\mu$ M was added to the perfusion chamber. The recording shown in Fig. 5 (on the right) was taken after 5 minutes perfusion with adrenaline. Adrenaline caused a 20% increase in the basal contraction force of the muscle. When the NT signal was turned on there was an additional 86% increase in the peak contraction force. This result indicates that high adrenaline concentration does not attenuate the increase in muscle contraction after NT signal stimulation.

Parameters:

Pacing: 1Hz, 2mS duration, 3mA.

NT signal was: 30mS delay, 60mS duration, 6mA.

### Example 6

#### Stimulation in the presence of Diltiazem

An experiment was carried out on a rabbit papillary muscle, in the presence of Diltiazem (a Ca-channel blocker commonly used in clinical treatment in ischemic heart disease), and the results are shown in Fig. 6.

A rabbit papillary muscle was stimulated in Organ-Bath perfused by KRS and 10  $\mu$ M Diltiazem, (Lot 702663). The NT-signal applied to this preparat produced an average increase in peak force of 20% under these experimental conditions. The drug caused a significant reduction in the basal contraction force of the muscle.

#### Parameters:

Pacing: 1 Hz, 2mS Duration, 1mA.

NT Signal: 50mS Delay, 50mS Duration, 4mA.

Temp. 36.2°C

### Example 7

#### Stimulation in the presence of Digoxin

An experiment was carried out on a rabbit papillary muscle, in the presence of Digoxin, and the results are shown in Fig. 7.

There is a 115% increase in the NT-signal induced force on the control without the addition of the drug. Addition of Digoxin caused an increase of

38% of the basal contraction force. Applying the NT-signal on the Digoxin-treated muscle caused a further increase of 86% on the new basal level, after 19 minutes treatment with Digoxin. The combined Digoxin-NT signal treatment is synergistic, and the increase in muscle contraction, as compared to the single contributions of each treatment, is 20%, as shown in the graph.

Pacing: 1Hz, 2 mS, 3 mA.

NT Signal: 1 Hz, delay 30 mS, duration 60 mS.

Referring now to Fig. 8, a schematic representation of an apparatus according to one embodiment of the invention is seen. In this scheme, a portion of a cardiac muscle, H, is brought into closed positioned relationship with two electrodes, E1 and E2, the ends of which are positioned at root position R1 and R2, respectively. The electrodes receive the voltage and current from a signal generator S, the construction of which is conventional and well known to skilled persons, and which is therefore not described here in detail, which in turn receives power from a power line, PL, connected to an autonomous power source or to the mains, as the case may be. The activity of the power signal generator S is controlled by a controller, C, which may be a microprocessor, or which may be an external controlling device, e.g., a PC or the like computer. The controller C controls the parameters of the signal generated by the signal generator, such as current intensity, frequency and timing, and may use

both preset parameters (e.g., the frequency of pulse generation) and feedback input, e.g., from apparatus which monitors heart or other parameters, or from a pace maker which supplies the pacing signal. These input signals are collectively schematically indicated in the figure as FB. Of course, the apparatus is only schematically shown, for the sake of brevity. And the skilled person will easily be able to devise many different kinds of apparatus suitable to supply the signal needed in carrying out the invention.

All the above description and examples have been given for the purpose of illustration and are not intended to limit the invention in any way. Many modifications can be carried out in the invention: for instance, many different drugs can be used in conjunction with an NT-signal, or different combinations of drugs can be used; furthermore, different signals can be employed, all without exceeding the scope of the invention.

### Claims

1. Apparatus for the combined drug/electric stimulation treatment of a cardiac muscle, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of a muscle.
2. Apparatus as claimed in claim 1, comprising circuitry for controlling the start time of the electric potential generated between said at least two points.
3. Apparatus as claimed in claim 1, comprising circuitry for controlling the duration of the electric potential generated between said at least two points.
4. Apparatus as claimed in claim 1, comprising circuitry for controlling the magnitude of the electric potential generated between said at least two points.
5. Apparatus as claimed in claim 1, wherein the circuitry for creating a non-excitatory electric potential between said at least two points comprises one or more electrode.
6. Apparatus as claimed in claim 5, wherein the electrodes are carbon electrodes.

7. Apparatus as claimed in claim 1, which is an insertable device.
8. Apparatus as claimed in claim 1, which is an extra corporal device.
9. Apparatus as claimed in claim 1, which is an implantable device.
10. Apparatus as claimed in claim 2 or 3, wherein the circuitry for controlling the start time and/or duration of the electric potential is synchronized to heart activity.
11. Apparatus as claimed in claim 10, wherein the circuitry for controlling the start time and/or duration of the electric potential operate not at every beat of the heart.
12. Apparatus as claimed in claim 11, wherein the circuitry for controlling the start time and/or duration of the electric potential operates every 1, 2 or 3 beats of the heart.
13. Apparatus for the combined drug/electric stimulation treatment, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of a muscle.

14. Apparatus as claimed in claim 13, comprising circuitry for controlling the start time of the electric current flowing between said at least two points.

15. Apparatus as claimed in claim 13, comprising circuitry for controlling the duration of the electric current flowing between said at least two points.

16. Apparatus as claimed in claim 13, comprising circuitry for controlling the magnitude of the electric current flowing between said at least two points.

17. Apparatus as claimed in claim 13, wherein the circuitry for causing a non-excitatory electric current to flow between said at least two points comprises one or more electrode.

18. Apparatus as claimed in claim 17, wherein the electrodes are carbon electrodes.

19. Apparatus as claimed in claim 13, which is an insertable device.

20. Apparatus as claimed in claim 13, which is an extra corporal device.

21. Apparatus as claimed in claim 13, which is an implantable device.
22. Apparatus as claimed in claim 14 or 15, wherein the circuitry for controlling the start time and/or duration of the electric current is synchronized to heart activity.
23. Apparatus as claimed in claim 22, wherein the circuitry for controlling the start time and/or duration of the electric current operate not at every beat of the heart.
24. Apparatus as claimed in claim 23, wherein the circuitry for controlling the start time and/or duration of the electric current operates every 1, 2 or 3 beats of the heart.
25. Apparatus as claimed in any one of claims 1 to 24, wherein the non-excitatory electric current is a DC electric current.
26. Apparatus for the combined drug/electric-stimulation treatment of a cardiac muscle, comprising:
- means for creating an electric potential between at least two points located in the vicinity of the cardiac muscle;
  - means for causing a non-excitatory electric current to flow between said at least two point; and



- means for controlling the start time, duration and magnitude of the electric current flowing between said at least two points.

27. Apparatus according to claim 26, comprising:

- means for creating an electric potential between at least a pair of electrodes in the vicinity of the cardiac muscle at at least two root locations;

- means for causing a non-excitatory electric current to flow between said at least two root locations; and

- means for controlling the start time, duration and magnitude of the electric current flowing between said at least two root locations.

28. Apparatus according to claim 26 or 27, further comprising means for superimposing on the DC signal one or more waveforms of given frequency and amplitude, thereby to generate a complex signal.

29. A method for the combined drug/electric stimulation treatment of a cardiac muscle, comprising a) administering to a patient in need thereof a drug which affects the cardiovascular system and which affects the cardiac muscle, or a mixture of two or more such drugs, b) creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and c) controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points.

30. A method for the combined drug/electric stimulation treatment of a cardiac muscle, comprising a) administering to a patient in need thereof a drug which affects the cardiovascular system and which affects the cardiac muscle, or a mixture of two or more such drugs, b) causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and c) controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points.

31. A method according to claim 30, wherein the non-excitatory electric current is a DC current.

32. A method according to claim 31, further comprising generating a complex signal by superimposing on the DC signal one or more waveforms of given frequency and amplitude.

33. A method according to any one of claims 30 to 32, wherein the flow of the non-excitatory DC electric current is synchronized to heart activity.

34. A method according to claim 33, wherein the non-excitatory DC electric current flows not at every beat of the heart.

35. A method according to claim 34, wherein the non-excitatory DC electric current flows every 1, 2 or 3 beats of the heart.

36. A method for the combined drug/electric-stimulation treatment of a cardiac muscle, comprising:

- administering to a patient in need thereof a drug which affects the cardiovascular system and which affects the cardiac muscle, or a mixture of two or more such drugs;

- providing means for creating an electric potential between at least two points located in the vicinity of the cardiac muscle;

- providing means for causing a non-excitatory electric current to flow between said at least two point; and

- controlling the start time, duration and magnitude of the electric current flowing between said at least two points so as to impart a desired change in cardiac muscle contractility.

37. A method according to any one of claims 29 to 36, wherein the change in cardiac muscle contractility is designed at least partially to compensate for cardiac muscle contractility decrease induced by said drug or mixture of drugs.

38. A method according to any one of claims 29 to 36, wherein the change in cardiac muscle contractility is designed at least partially to compensate

for cardiac muscle contractility increase induced by said drug or mixture of drugs.

39. A method according to any one of claims 29 to 36, wherein the change in cardiac muscle contractility is designed to add to and/or amplify the cardiac muscle contractility increase or decrease induced by said drug or mixture of drugs.

40. A method according to any one of claims 29 to 36, for reducing the dosage of a cardiovascular drug which affects cardiac muscle contractility.

41. A method according to any one of claims 29 to 36, for reducing the dosage of a cardiovascular drug which affects the electrophysiological characteristics of the cardiac muscle.

42. A method for the combined drug/electric-stimulation treatment of a cardiac muscle, comprising:

- administering to a patient in need thereof a drug which affects the cardiovascular system and which affects the cardiac muscle, or a mixture of two or more such drugs;

- providing an electric potential between at least a pair of electrodes in the vicinity of the cardiac muscle at at least two root locations;

- causing a non-excitatory electric current to flow between said at least two contacting locations; and

- controlling the start time, duration and magnitude of the electric current flowing between said at least two root locations, so as to impart the desired change in cardiac muscle contractility.

43. A method according to claim 42, wherein the means for causing a non-excitatory electric current to flow, are synchronized to heart activity.

44. A method according to claim 43, wherein the means for causing a non-excitatory electric current to flow operate not at every beat of the heart.

45. A method according to claim 44, wherein the means for causing a non-excitatory electric current to flow operate every 1, 2 or 3 beats of the heart.

46. A kit for the treatment of cardiovascular diseases, comprising a drug or a combination of two or more drugs, and an apparatus according to any one of claims 1 to 29.

47. Apparatus as claimed in any one of claims 1 to 26, comprising circuitry for controlling its activity as a function of calculated and/or actual level of a given drug or combination of drugs in the patient's blood.

48. Apparatus according to any one of claims 1 to 26, for use in reducing the dosage of pro-arrhythmic drugs.

49. Apparatus according to any one of claims 1 to 26, for use in counteracting side-effects of pro-arrhythmic drugs.

50. Apparatus according to any one of claims 1 to 26, comprising timing circuitry for activating it at predetermined times during the day.

51. A method for the combined drug/electric-stimulation treatment of a cardiac muscle, essentially as described and with particular reference to the examples.

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FORCE 0.5 gr

20 s

CAFFEINE 10mM

NT Signal

NT Signal

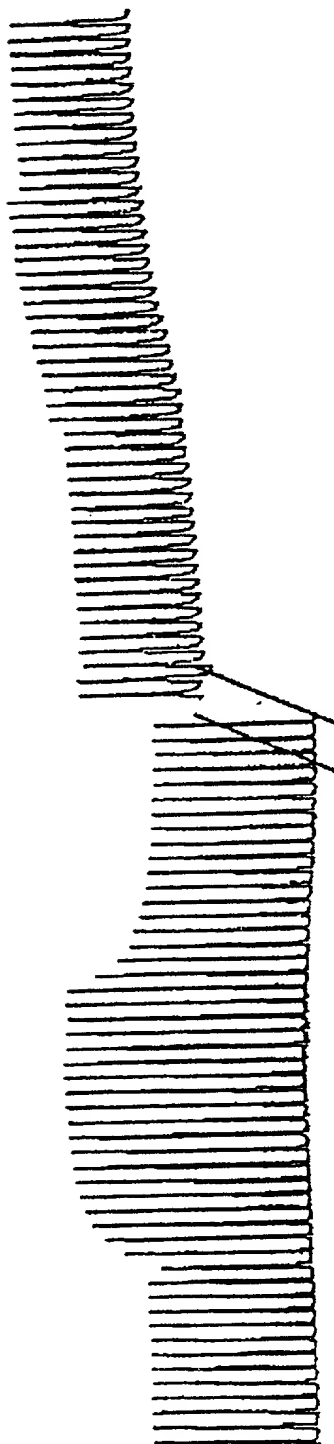


Fig. 1

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FORCE 0.5 gr

RYANODINE 100nM

NT Signal

NT Signal

50 s

Fig. 2



NIFEDIPINE 1 $\mu$ M

NT Signal

NT Signal

FORCE 0.5 gr

50 s

Fig. 3

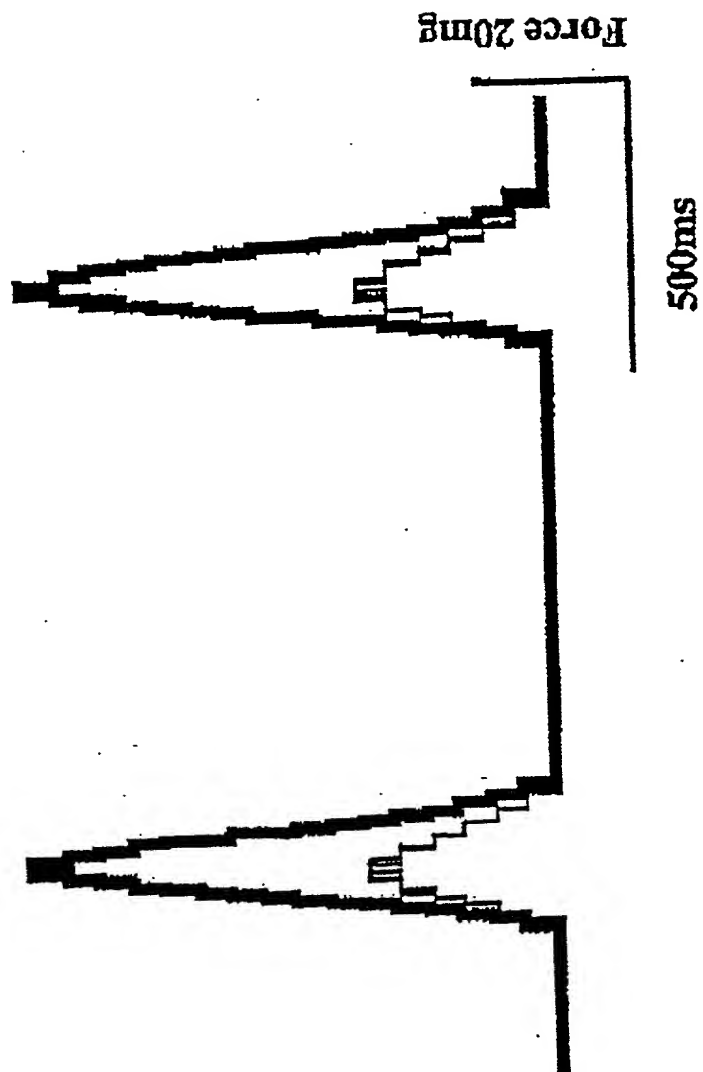


Fig. 4

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09/254993

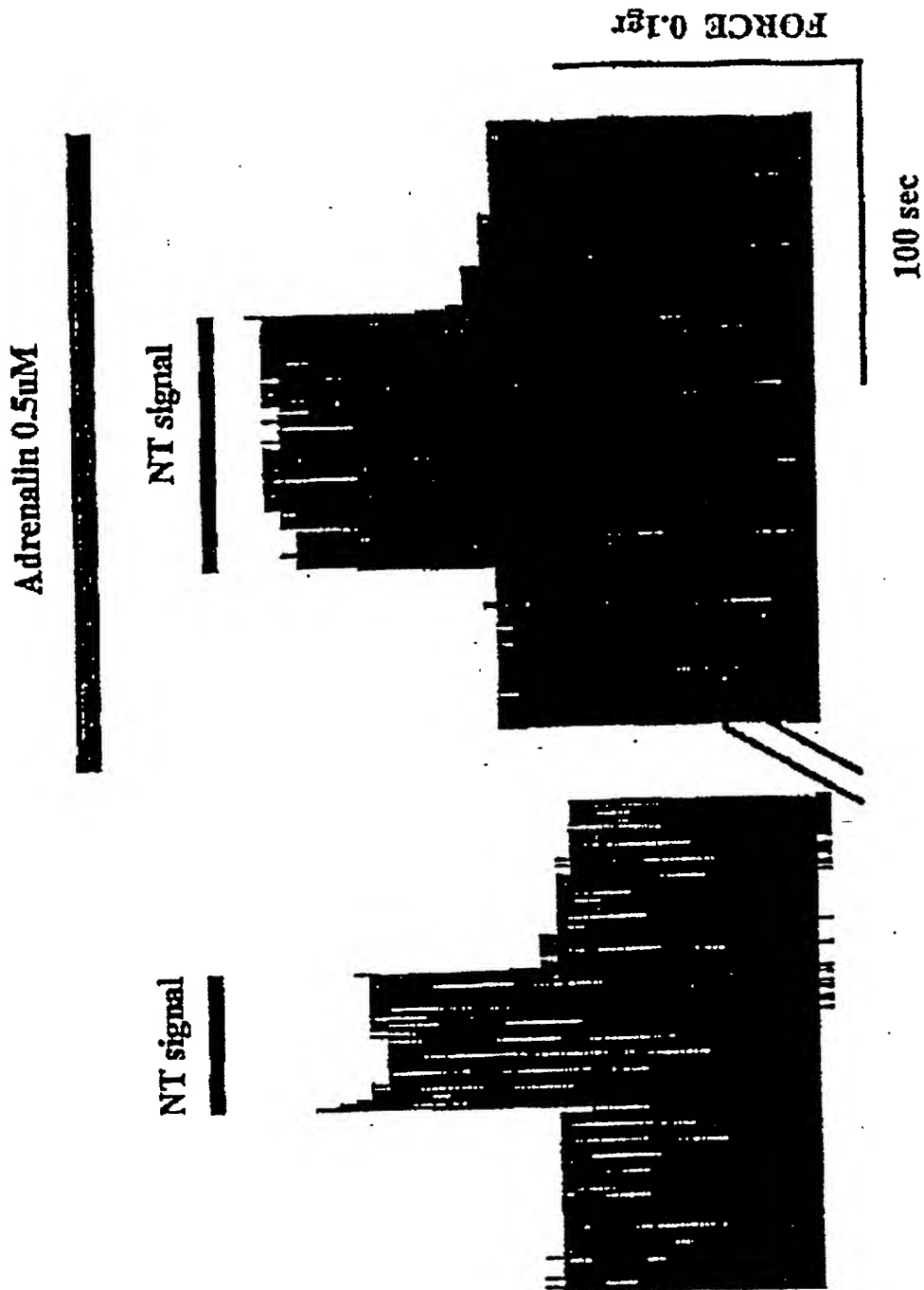
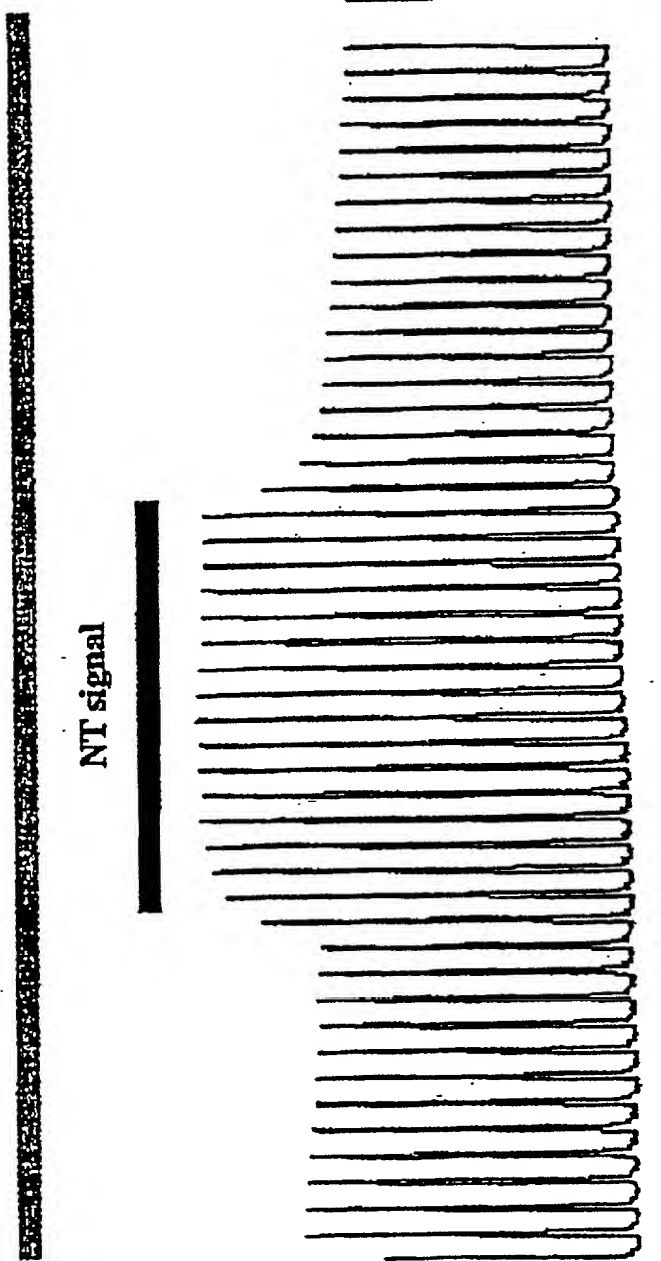


Fig. 5

Diltiazem, 10 uM

NT signal



FORCE 0.1 gr

10 sec

Fig. 6

Digoxin 0.5 $\mu$ M

NT Signal

NT Signal

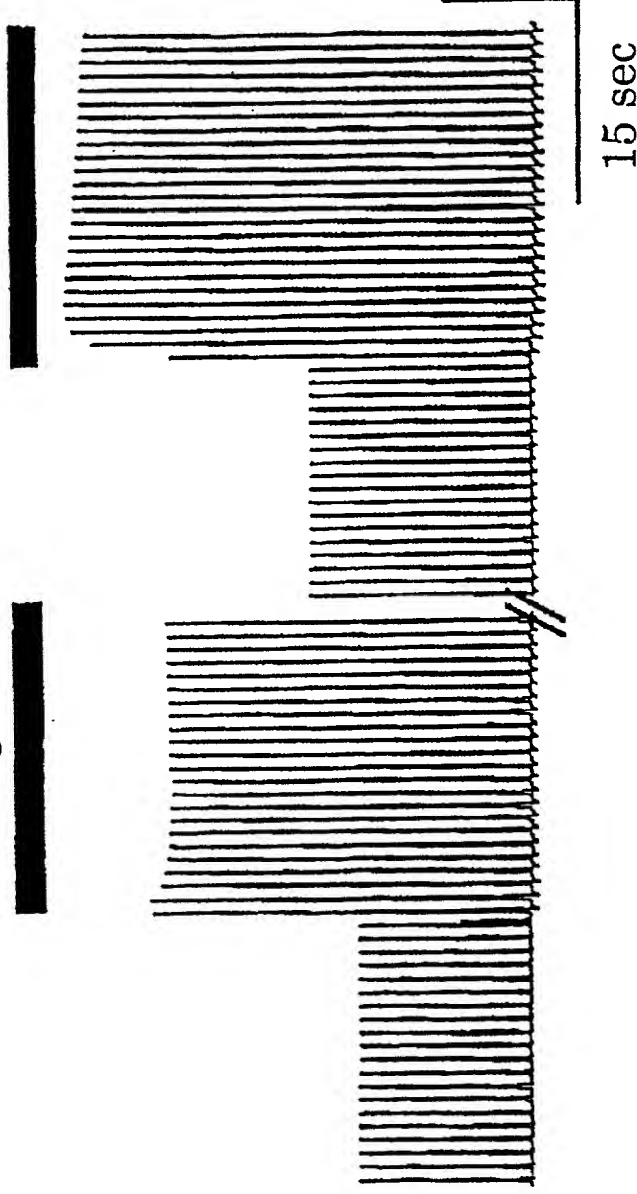


Fig. 7

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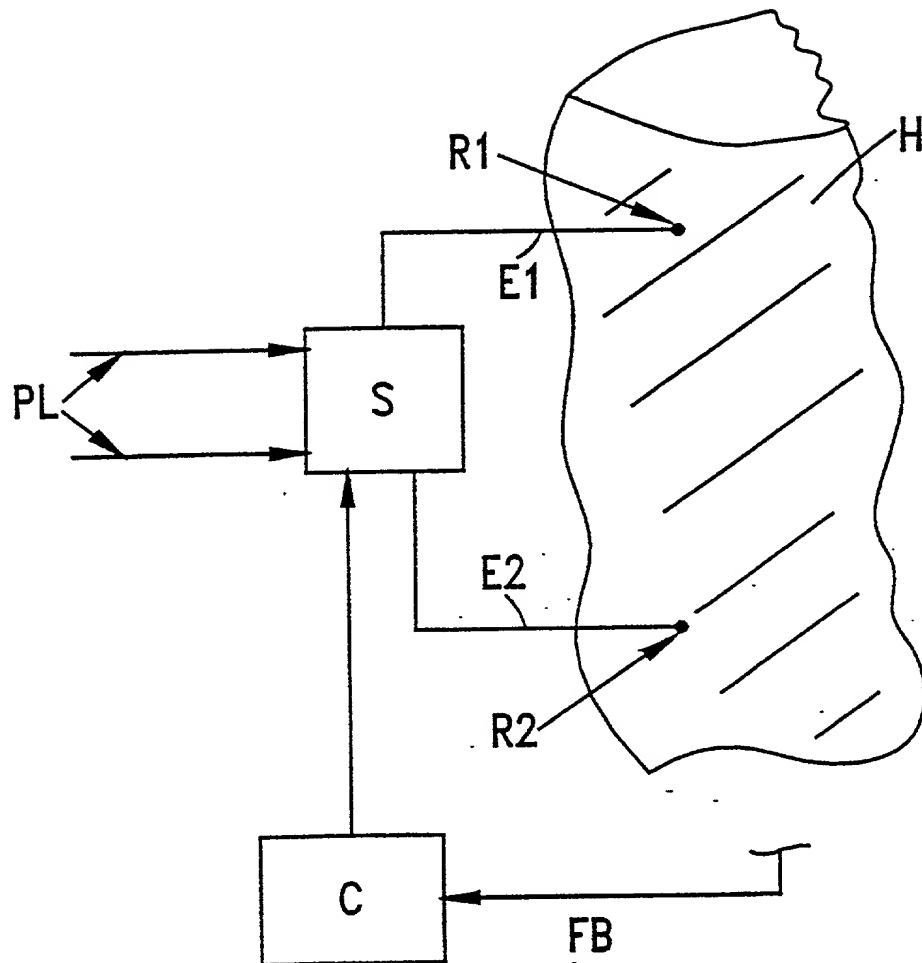


Fig. 8

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	<b>First Named Inventor</b>	Shlomo BEN-HAIM et al
	<b>COMPLETE IF KNOWN</b>	
	<b>Application Number</b>	/ to be assigned
	<b>Filing Date</b>	to be assigned
	<b>Group Art Unit</b>	
	<b>Examiner Name</b>	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**DRUG-DEVICE COMBINATION FOR CONTROLLING THE CONTRACTILITY OF MUSCLES**

the specification of which (Title of the Invention)

☒ is attached hereto  
OR

☐ was filed on (MM/DD/YYYY) as United States Application Number or PCT International

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I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
119261	Israel	09/17/1996	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.
60/026,392	09/16/1996	

[Page 1 of 2]

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## DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/IL97/00232	07/09/1997	

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William H. Dippert	26,723	Morey B. Wildes	36,968
R. Lewis Gable	22,479		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label

OR ☒ Correspondence address below

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City	New York	State	NY	ZIP	10036-6799
Country	USA	Telephone	(212) 790-9200	Fax	(212) 575-0671

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Name of Sole or First Inventor:

☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))		Family Name or Surname	
Shlomo		BEN-HAIM	
Inventor's Signature	Date		
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			Israel
Citizenship	ISR		
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Post Office Address			
City	Haifa	State	ZIP
			34454
Country	Israel		

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<b>Name of Additional Joint Inventor, if any:</b>		<input type="checkbox"/> A petition has been filed for this unsigned inventor					
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# DECLARATION

## ADDITIONAL INVENTORS Supplemental Sheet Page 1 of 1

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## DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 119 of the United States application(s) or world of any PCT international application(s) designating the United States of America, listed below and, insofar as the subject matter of each of its claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the last paragraph of 35 U.S.C. 112, I acknowledge the duty to declare information which is material to patentability as defined in 37 C.F.R. 1.55 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/AL87/D0082	07/03/1987	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet (PTA/350/2) attached hereto.

As an applicant, inventor, I hereby appear and following registered practitioner(s) to prosecute this application and to conduct all business in the Patent and Trademark Office connected herewith:

Name	Registration Number	Name	Registration Number
Michael L. Wolfson	24,750	Frank J. DeRose	28,543
William H. Dippert	26,725	Mervyn B. Wildes	28,588
R. Lewis Gable	22,479		

☐ Additional registered practitioners named on supplemental Registered Practitioner Information sheet (PTA/350/3) attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label ☒ Correspondence address below

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that false statements and the do so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:		<input type="checkbox"/> A petition has been filed for this unsigned inventor	
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☒ Additional inventors are being named on the 1 supplemental inventor(s) sheet(s) (PTA/350/4) attached hereto.